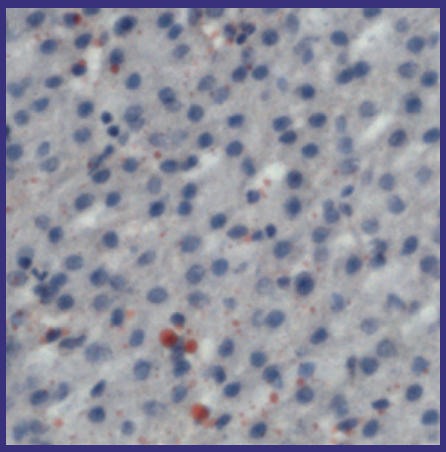

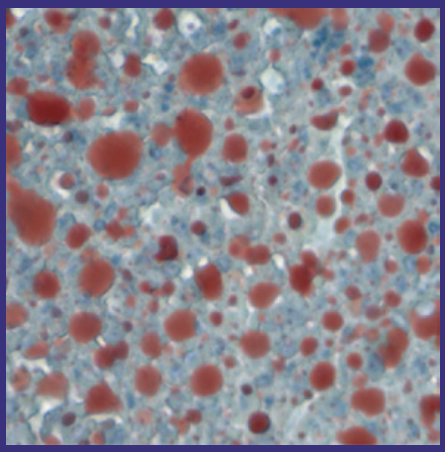

Nonalcoholic fatty liver disease, a condition that resembles alcoholic liver disease but occurs in patients who drink little or no alcohol, is an increasingly important cause of liver failure and occurs in a high proportion of persons with diabetes. The disease is associated with overweight and obesity, and abnormal fat in the liver is also associated with the metabolic problem of insulin resistance. NIDDK-supported research highlighted in this chapter sheds new light on the effects of a high-fat diet during pregnancy on liver disease in offspring. For example, a recent study in non-human primates suggests that a chronic high-fat diet results in a significantly increased risk of fetal fatty liver disease that persists after birth. One striking example of increased fatty liver disease risk in offspring comes from examining the amount of fat stored in the liver cells from offspring of animals fed a low-fat diet (left) and a high-fat diet (right). The liver cells of offspring from animals fed a high-fat diet contained significantly greater amounts of fat (stained red) compared to those fed a low-fat diet, indicative of fatty liver disease development. Recognition of the role of the prenatal environment in the genesis of fatty liver suggests a potential approach to prevent the disorder. In addition to studies in animals, the NIDDK's Nonalcoholic Steatohepatitis (NASH) Clinical Research Network recently conducted two clinical trials that examined nonalcoholic fatty liver disease in children and adults. This chapter contains additional information about the impact of high-fat diets and other recent research on obesity and its associated diseases.

Obesity

Obesity has risen to epidemic levels in the U.S. Individuals who are obese may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within the NIDDK's mission.

Approximately one-third of U.S. adults are considered obese based on body mass index (BMI), a measure of weight relative to height.[1,2] Moreover, while obesity and overweight have risen in the population in general, the greatest increases observed over approximately the past 2 decades have been in the prevalence of extreme obesity; those who are severely obese are most at risk for serious health problems.[3] Levels of childhood overweight and obesity have also escalated in the past several decades. Obesity affects approximately 16 percent of children and teens ages 2 through 19.[1,4,5] These children are at risk for developing serious diseases both during their youth and later in adulthood. Overweight and obesity also disproportionately affect racial and ethnic minority populations, and those who are socio-economically disadvantaged.

The increased prevalence of obesity in the U.S. is thought to result from the interaction of genetic susceptibility with behavior and factors in the environment that promote increased caloric intake and sedentary lifestyles. Thus, the NIDDK supports a multi-dimensional research portfolio on obesity, ranging from basic studies to large clinical trials. These studies have led to many important advances in our understanding of both the causes of obesity and in potential interventions for prevention and treatment. For example, researchers recently discovered the existence of brown fat tissue in adults, a finding with potential therapeutic implications. This metabolically active tissue burns fat molecules to generate heat, and in humans was once thought to exist only in infants. Other studies are looking at how the nutrients we eat may signal the brain to indicate fullness. A study in rodents revealed that a type of fat secreted into the blood from the small intestine in response to a high-fat meal may be linked to the ability to suppress appetite. Scientists are continuing to investigate the origins and development of fat cells with the goal of developing new therapies to combat obesity and type 2 diabetes. Other research includes observational studies to evaluate the risks and benefits of bariatric surgery as a treatment for severe obesity, as well as studies of behavioral and environmental interventions to reduce obesity in children and adults.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. To help bring the results of research to the public and health care providers, the NIDDK also sponsors education and information programs. Given the importance of the obesity epidemic as a public health problem, and its relevance to the mission of the NIDDK, the Institute continues to play a leading role in the NIH Obesity Research Task Force. Co-chaired by the Directors of the NIDDK and the National Heart, Lung, and Blood Institute, the Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices. With extensive input from external scientists and the public, the Task Force developed the *Strategic Plan for NIH Obesity Research*, published in 2004. In light of the many discoveries in the past several years, NIH scientists are currently in the process of updating the *Strategic Plan* and will be receiving input from

[1] *Statistics Related to Overweight and Obesity. http://win.niddk.nih.gov/statistics/index.htm*

[2] *Ogden CL, et al: JAMA 295: 1549-1555, 2006; Ogden CL, et al: NCHS Data Brief 1: 1-8, 2007.*

[3] *Flegal KM, et al: JAMA 288: 1723-1727, 2002; Flegal KM and Troiano RP: Int J Obes Relat Metab Disord 24: 807-818, 2000; Freedman DS, et al: JAMA 288: 1758-1761, 2002.*

[4] *Ogden CL, et al: JAMA 299: 2401-2405, 2008.*

[5] *For children and adolescents, this document uses the term obesity to refer to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).*

external reviewers. Through this broad spectrum of research efforts, the NIDDK will continue to augment understanding of obesity and develop and test prevention and treatment approaches to improve health.

GENETICS OF OBESITY

Multiple Genetic Variations Linked to Overall Body Fat and Fat Distribution: By analyzing DNA from thousands of individuals, researchers have identified variations in multiple regions of the genome associated with common measures of obesity regarding total body fat and fat distribution. Although factors such as poor diet and lack of exercise are important contributors to obesity, genetic factors also help determine whether or not an individual is likely to become obese in a given environment. Past research on families and twins demonstrated that genetic factors account for much of the variation in body mass index (BMI), a common measure of body "fatness," across a population. In addition to BMI, other important measures of obesity, including waist size and the ratio of waist size to hip size, are believed to have a genetic component as well. To identify genetic factors associated with measures of obesity, an international consortium of researchers supported by NIDDK and others analyzed data from several, large-scale genome-wide association studies (GWAS). In GWAS, scientists scan the genomes of many individuals to look for genetic variations associated with a particular trait or condition, such as obesity.

Previous studies had identified common variants in two gene regions—or loci—that are believed to influence BMI. For one study of combined GWAS data, researchers looked for genetic variations associated with BMI regulation in more than 32,000 individuals of European ancestry. From this analysis, they uncovered genetic variations in or near six previously unreported gene loci that were reproducibly associated with adult BMI. Of the six BMI-related loci, five contain genes that are highly active in the region of the brain that regulates hunger, thirst, body temperature, fatigue, and circadian rhythms. These findings are consistent with the multiple possible roles of the central nervous system in controlling body weight, including regulation of appetite, energy expenditure, and other behavioral aspects.

Along with BMI, fat distribution—in particular, abdominal fat—has emerged as an important predictor of the risk of developing obesity-related disorders such as type 2 diabetes and heart disease. In a second analysis of data from several GWAS, scientists identified genetic variations that are associated with waist circumference or waist-to-hip ratio as measures of abdominal fat distribution. In addition to identifying some of the variants already associated with BMI, this study found novel variants in two loci that were strongly associated with waist size. One of the loci is near a gene called *TFAP2B*, which codes for a protein that is involved in regulating the accumulation of fat in fat cells. An additional variant near a third gene—*LYPLAL1*—was found to be associated with the waist-to-hip measure of fat distribution in women, but not in men. These results complement the findings of genetic variations associated with BMI, and identify some of the genetic components that regulate fat distribution in obesity, potentially identifying the genetic contributors to a subgroup at high risk for obesity-related diseases.

These two analyses of large, genome-wide studies have identified a number of novel genetic factors that are associated with measures of obesity. In most cases, further experiments will be needed to determine or confirm which genes—within the regions marked by the identified variants—have causal effects on obesity, and the mechanisms by which they contribute to obesity. Nonetheless, identification of these genes and gene loci provides new insights into the biological processes that regulate body weight and fat distribution, which may lead to the development of new therapeutic strategies for obesity.

Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lim N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccasecca RM, Sanna S, Scheet P, Weedon MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burtt NP, Chines P, Coin L, Collins FS, Connell JM, Cooper C, Smith GD, Dennison EM, Deodhar P, Elliott P, Erdos MR, Estrada K, Evans DM, Gianniny L, Gieger C, Gillson CJ, Guiducci C, Hackett R, Hadley D, Hall AS, Havulinna AS, Hebebrand J, Hofman A, Isomaa B, Jacobs KB, Johnson T, Jousilahti P, Jovanovic Z, Khaw KT, Kraft P, Kuokkanen M, Kuusisto J, Laitinen J, Lakatta EG, Luan J, Luben

RN, Mangino M, McArdle WL, Meitinger T, Mulas A, Munroe PB, Narisu N, Ness AR, Northstone K, O'Rahilly S, Purmann C, Rees MG, Ridderstråle M, Ring SM, Rivadeneira F, Ruokonen A, Sandhu MS, Saramies J, Scott LJ, Scuteri A, Silander K, Sims MA, Song K, Stephens J, Stevens S, Stringham HM, Tung YC, Valle TT, Van Duijn CM, Vimaleswaran KS, Vollenweider P, Waeber G, Wallace C, Watanabe RM, Waterworth DM, Watkins N; Wellcome Trust Case Control Consortium, Witteman JC, Zeggini E, Zhai G, Zillikens MC, Altshuler D, Caulfield MJ, Chanock SJ, Farooqi IS, Ferrucci L, Guralnik JM, Hattersley AT, Hu FB, Jarvelin MR, Laakso M, Mooser V, Ong KK, Ouwehand WH, Salomaa V, Samani NJ, Spector TD, Tuomi T, Tuomilehto J, Uda M, Uitterlinden AG, Wareham NJ, Deloukas P, Frayling TM, Groop LC, Hayes RB, Hunter DJ, Mohlke KL, Peltonen L, Schlessinger D, Strachan DP, Wichmann HE, McCarthy MI, Boehnke M, Barroso I, Abecasis GR, and Hirschhorn JN, for the Genetic Investigation of ANthropometric Traits Consortium: Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 41: 25-34, 2009.

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MOLECULAR REGULATORS OF METABOLISM

Metabolic Regulation by the Immune System: New research may help break the link between obesity and diabetes. Although overweight and obesity confer significant risk for developing type 2 diabetes, the precise mechanisms underlying the relationship between body fat and diabetes remain unclear. An accumulation of research over the last several years, however, implicates the chronic, low-grade inflammation that typically accompanies obesity in promoting insulin resistance, which is a precursor to type 2 diabetes. Earlier work found a type of immune system cell, the macrophage, is abundant in the fat tissues of obese mice (and humans). Macrophages are responsible for producing some of the chemical signals that trigger the inflammatory response. Now, new research finds that a different type of immune system cell—called $CD4^{+}Foxp3^{+}$ Regulatory T (Treg) cells—are found in the fat of lean animals, but not in those that are overweight. Experimentally depleting Treg cells from lean mice increased their resistance to insulin. Importantly, the researchers found that the Treg cells produce chemical signals that attenuate the inflammatory response when experimentally introduced into fat mice, helping restore the animals to a more normal metabolic state. This suggests that restoring normal immune regulatory signals in people at risk for type 2 diabetes may one day interrupt the development of insulin resistance and help to prevent the disease.

Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, and Mathis D: Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 15: 930-939, 2009.

Cells Self-Digest To Burn Fat for Energy When Starved: Scientists have discovered that cells use a 'self-destruction' pathway to burn fat for energy during times of nutrient starvation. When nutrients

are scarce, cells turn on metabolic pathways that mobilize stores of fat as a source of energy to carry out necessary cellular functions. Molecules of fat known as triglycerides (TGs), together with cholesterol, are stored in cellular compartments called "lipid droplets." The composition of lipid droplets is normally dynamic, where TGs are continuously broken down into their component parts—free fatty acids—and reassembled into TGs for storage depending on the cell's energy needs. During times of starvation, cells trigger the breakdown of TGs into free fatty acids, which serve as fuel for the cell.

In a recent study supported by NIDDK, scientists demonstrated that the breakdown of TGs during nutrient deprivation is mediated, in part, by a cellular process known as autophagy. Autophagy, which translates literally as "to eat oneself," is a complex metabolic process in which cellular components are packaged and delivered to cellular depots called lysosomes. Material destined for destruction in the lysosome is broken down and recycled for other purposes. In addition to the previously known role for autophagy in general cellular "housekeeping," it now appears that autophagy also plays an important role in breaking down fats in the liver during starvation. To explore the link between autophagy and processing of fats, the scientists used pharmacologic agents and genetic engineering to block autophagy in laboratory-grown liver cells or in the livers of mice, and found that TGs and lipid droplets accumulated. In addition, by examining the cells microscopically under various experimental conditions, the researchers found that components of the autophagy machinery associate with lipid droplets and deliver the droplets to the lysosome for destruction. In mice, the autophagy-mediated destruction of lipid droplets was activated following prolonged nutrient starvation. When mice are fed a high-fat diet, on the other hand, the excess fat appears to inhibit the autophagy pathway and, in a cyclical fashion, further increase fat accumulation. This is of clinical importance, as the decrease in autophagic function with aging may contribute to the accumulation of fat in the liver associated with a constellation of health problems referred to as the metabolic syndrome. Therapeutic strategies that stimulate autophagy to promote the breakdown of fats in the liver may, therefore, be a useful approach for preventing metabolic syndrome.

Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, and Czaja MJ: Autophagy regulates lipid metabolism. Nature 458: 1131-1135, 2009.

Controlling Metabolism with Genes: A new study has found that a protein called Jhdm2a is able to control body weight in mice by turning on or turning off genes involved in metabolism. Jhdm2a does this by modifying a protein that packages DNA. In a cell, DNA molecules are wrapped around proteins called histones. Changing the way that the DNA molecule wraps around a histone, or the structure of the histone itself, can change the way genes are turned on or off. One way that this DNA-protein interaction can change is through chemical modification of a histone. One factor known to chemically alter histones is Jhdm2a. Previously, this factor was shown to have an important role in a different process: the development of sperm in mice. Interestingly, when examining an experimental mouse model that lacked Jhdm2a, a group of scientists recently noticed that these mice became obese in adulthood, as compared to normal animals. Turning their attention to a potential role for Jhdm2a in body weight, the researchers designed further experiments that revealed that Jhdm2a protein levels are high in organs involved in metabolism, such as brown fat tissue and muscle. These observations led the scientists to speculate that Jhdm2a plays an important role in regulating metabolism.

To better understand the role of Jhdm2a in controlling metabolism, the researchers decided to conduct additional studies of mice lacking this protein. Without Jhdm2a, the mice accumulated large droplets of fat in their fat tissue cells as well as in other organs, such as liver and muscle, and they also had high levels of fat in their blood despite eating a normal diet. These results suggested that a lack of Jhdm2a results in abnormal fat metabolism and obesity. Subsequent experiments revealed that the absence of Jhdm2a protein led to the gene *Ppar-alpha* being turned off; this gene plays a key role in fat metabolism in skeletal muscle. The scientists also determined that another gene important in controlling energy balance, *Ucp1*, is not activated normally in the brown fat of mice lacking Jhdm2a protein. One metabolic result of this defect is that the mice without Jhdm2a were unable to maintain body temperature as well as normal mice in cold temperatures, likely because their brown fat

could not burn energy to generate heat as efficiently. Additional studies showed that the absence of Jhdm2a protein resulted in cells failing to turn on other factors necessary for *Ucp1* activity. Given these results, the researchers proposed that Jhdm2a mediates certain cell signaling pathways based on systemic energy demands, and is thus a key regulator of energy balance and body weight. Although the precise manner by which Jhdm2a controls metabolism is not yet completely understood, this study may lead to novel approaches for obesity prevention or treatment.

Tateishi K, Okada Y, Kallin EM, and Zhang Y: Role of Jhdm2a in regulating metabolic gene expression and obesity resistance. Nature 458: 757-761, 2009.

SMRT Mice—Discovering Molecular Controls of Metabolism: Scientists have discovered that a protein called SMRT, which is involved in turning various genes off, plays a major role in regulating metabolism and fat cell formation. Metabolism is a complex and carefully regulated process that involves turning numerous genes on or off (called "gene expression"). Nuclear hormone receptors (NHRs) are proteins that moderate a wide variety of biological processes by controlling gene expression, and are known to have critical roles in regulating metabolism and development. NHRs control gene expression, in part, by interacting with proteins called "corepressors," which prevent genes from being turned on. However, the precise function of NHR-interacting corepressors, and the role corepressors may play in metabolism, is not well understood.

The SMRT protein is a corepressor known to be involved in cellular and organ development. It was believed to require interaction with NHRs for at least some of its activities. Reducing or eliminating levels of SMRT in mouse models results in brain and heart defects and death during embryonic development. To further examine the role of SMRT and its interaction specifically with NHRs, scientists generated a genetically-engineered mouse in which SMRT is present but unable to physically interact with NHRs. Interestingly, although these mice lived and had normally developed organs, they displayed a number of metabolic disorders. The mice had significantly decreased metabolic rates and developed factors predisposing them to type 2 diabetes, including high blood glucose levels and insulin resistance.

Moreover, the mice had significantly increased volumes of fat tissue due to an increased number of fat cells. Fat cells, or "adipocytes," are believed to be derived from stem cells known as fibroblasts. Under normal circumstances, a small fraction of mouse embryonic fibroblasts will develop into adipocytes when exposed in the laboratory to a combination of proteins or chemicals. When researchers isolated embryonic fibroblasts from the genetically-engineered mice, however, and treated these cells with a mixture of reagents known to induce conversion into adipocytes, nearly all the fibroblasts became mature adipocytes. More surprisingly, researchers discovered that embryonic fibroblasts isolated from the mice were able to spontaneously turn into adipocytes without exposure to the reagents. Additionally, the researchers found that cells with the altered SMRT proteins had increased levels of expression of key fat cell genes. These experiments led scientists to conclude that SMRT is a critical factor in determining whether an embryonic fibroblast will develop into a fat cell.

This research provides the first evidence that SMRT is required for metabolic balance. Likewise, SMRT also appears to regulate the development of adipocytes and fat tissue. These data suggest that various metabolic processes are influenced or controlled by NHR-SMRT interaction, and may provide future targets for pharmaceutical interventions to treat metabolic disorders.

Nofsinger RR, Li P, Hong SH, Jonker JW, Barish GD, Ying H, Cheng SY, Leblanc M, Xu W, Pei L, Kang YJ, Nelson M, Downes M, Yu RT, Olefsky JM, Lee CH, and Evans RM: SMRT repression of nuclear receptors controls the adipogenic set point and metabolic homeostasis. Proc Natl Acad Sci USA 105: 20021-20026, 2008.

GUT MICROBES, ADIPOSITY, AND OBESITY

Protein on Intestinal Cells Controls Use of Nutrients Digested by Microbes: Scientists have discovered how the intestines detect and absorb some of the nutrients—and the associated calories—that have

been processed from the diet by gut microbes. The ability of the human digestive system to metabolize nutrients is supplemented by the microbial community residing inside the intestines. This community provides an array of digestive functions, including breaking down dietary complex carbohydrates, which humans cannot digest on their own, into smaller molecules called short-chain fatty acids (SCFAs), which can readily be absorbed by the intestines and used as a source of energy. SCFAs resulting from microbial digestion are detected by a protein called Gpr41—a receptor that sits on the surface of cells lining the intestines. Yet, the details of how Gpr41 triggers cellular responses that regulate extraction of microbially produced nutrients, and how this might contribute to overall energy balance, were obscure.

To understand how Gpr41 detects and regulates use of SCFAs produced by intestinal microbes, NIDDK-supported scientists compared normal mice to genetically-engineered mice that lacked the Gpr41 protein. In addition to the genetic modifications, the scientists also manipulated the intestinal microbial communities of these mice by raising them either conventionally (with a full intestinal microbial community), under germ-free conditions (in which the intestine would be free of microbes), or initially germ-free followed by addition of two key microbes found in human intestine—*Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii*. Removing Gpr41 in mice that have either a full intestinal microbial community or just the two key microbes caused them to gain less weight (*i.e.*, extract fewer nutrients, and thus calories, from the same carbohydrate-rich diet as normal mice with Gpr41). The scientists demonstrated that this effect in Gpr41-deficient mice was associated with a decrease in production of a hormone called PYY, which controls gut motility. The lower levels of PYY hormone in Gpr41-deficient mice caused nutrients to pass through the digestive tract more quickly than in normal mice, resulting in less absorption of the SCFAs by the intestines and greater excretion from the body in waste.

The results of this study demonstrate that in normal mice with functioning Gpr41, detection of microbially produced SCFAs by this receptor causes a change in hormone levels that modulates how efficiently these nutrients are absorbed by the intestines and made available as an energy source. The microbial community in the intestine of obese mice is more efficient at converting carbohydrates to SCFAs and extracting energy from the diet. If Gpr41 functions similarly in humans, it could serve as a therapeutic target for decreasing nutrient absorption and thus reducing weight in obese individuals.

Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, and Gordon JI: Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci USA 105: 16767-16772, 2008.

Obesity Linked to Unique Mix of Intestinal Bacteria and Bacterial Genes: Scientists have discovered that bacteria that dwell in the human gut are associated with their host's obesity or leanness. This work provides clues to how knowledge of the gut microbial community might be used to counter human obesity. Bacteria that inhabit the gut—the gut microbiota—perform important functions, including breaking down food that could not otherwise be digested. Mouse studies have also suggested that bacterial diversity in the gut may influence whether animal "hosts" are lean or obese, based on differences in the efficiency of specific types of bacteria to extract energy (calories) from food.

In a recent study of obese and lean adult twin sets and their mothers, researchers studied the human microbiota using fecal samples to determine whether host obesity, genetics, or environment is associated with the bacterial composition of the microbiota. To determine which types of bacteria were present in the gut, the researchers analyzed DNA sequences in a particular gene common to all bacteria to identify sequence variations unique to each type. Comparisons revealed that the proportion of different types of bacteria in the guts of obese twins differed from that in the lean twins. *Actinobacteria* were more abundant than *Bacteriodetes* bacteria in the obese twins. Conversely, *Bacteriodetes* were more numerous in the lean twins. Obesity was also associated with significantly less bacterial diversity overall than leanness. Additional analysis revealed that the microbiota of family members are more similar in

bacterial composition than unrelated individuals. Surprisingly, the identical twins were not more similar in their gut microbes than fraternal twins, suggesting that composition of the gut microbiota is influenced more strongly by environmental factors than by an individual's genes. An analysis of bacterial genes represented in the "microbiome"—the combined DNA of the microbiota—found that although the precise composition of the types of bacteria in the gut differs among individuals, people share a "core microbiome" of common microbial genes harbored by the various bacteria. Additionally, comparison of non-core microbiome genes identified over 350 genes that were either enriched or depleted in the microbiomes of obese individuals. Among the genes enriched in the obese gut microbiome, many of which are involved in processing carbohydrates and other metabolic pathways, most were from *Actinobacteria* and others were from another group of bacteria, *Firmicutes*.

While this study does not demonstrate cause and effect—whether differences in human microbiota help cause obesity or leanness, or whether obesity or leanness leads to changes in gut microbes—earlier research has shown that the composition of gut microbiota can influence weight gain in mice. This study does demonstrate a significant link between obesity and the gut microbiome, including the identification of several hundred genes that represent biomarkers of unique gut bacterial activity in obese individuals. These biomarkers may lead to more personalized health care and potential probiotic interventions to modify the microbial content of the human gut.

Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, and Gordon JI: A core gut microbiome in obese and lean twins. Nature 457: 480-484, 2009.

NEW INSIGHTS INTO FAT

Finding Where Fat Comes From—Research on Fat Cell Precursors: A recent study has shed new light on how fat cells, also known as adipocytes, develop. Understanding fat tissue biology and how adipocytes develop will help scientists develop potential new therapies to combat obesity and diabetes. These metabolic disorders have reached epidemic levels, and the resulting public health crisis necessitates an understanding of fat tissue function. Fat cell development is a fundamental process that has important biological impacts. Fat cells develop from an immature cell type (precursor cell). However, little is known about the identity of these precursors, when they become destined or committed to give rise to fat cells, and precisely where they are located. The precursor cells are believed to reside in a specialized part of fat tissue called the stromal-vascular (SV) compartment. For a precursor cell to develop into a mature adipocyte, the precursor cell must produce (or "express") a protein known as PPAR-gamma. Because PPAR-gamma plays an integral role in fat cell development, scientists used this protein as a tool to study the precursors and observe how precursor cells transformed into fat cells. To do this, researchers created a genetically-engineered mouse in which any cell that produces PPAR-gamma is permanently marked so that it—and if it divides, any cell derived from it—can be easily identified. By studying these mice shortly after birth, the researchers discovered that the majority of the adipocytes in the mice were derived from a pre-existing pool of cells that express PPAR-gamma. Subsequently, the scientists determined that fat cells in the young mice developed from precursor cells that are present prior to birth and can replicate, and are the primary source of large numbers of fat cells that develop during the first month of life.

Further experiments determined that the SV compartment within fat tissue contains a large number of PPAR-gamma-expressing cells that are able to divide and provide a source of precursor cells that in turn mature into adipocytes. These PPAR-gamma-expressing cells reside in tubelike structures that appear to be blood vessels within the SV compartment of white fat deposits. Detailed analysis revealed that the PPAR-gamma-expressing cells in these vessels represent a unique population within fat tissue and are biologically distinct from fully developed adipocytes. Interestingly, when these PPAR-gamma-expressing cells were isolated from the SV compartment in fat tissue and transplanted into other mice, the cells could be chemically induced to develop into mature adipocytes. This indicated that the PPAR-gamma-expressing cells isolated from the

fat tissue SV compartment have the unique ability to develop into adipocytes and serve as a source of fat cells. Collectively, these studies indicate that the interaction between fat tissue and the SV compartment could potentially provide targets for future therapies to treat obesity and diabetes. Understanding the process of adipocyte development can help identify future strategies to preempt disease and metabolic disorders.

Tang W, Zeve D, Suh JM, Bosnakovski D, Kyba M, Hammer RE, Tallquist MD, and Graff JM: White fat progenitor cells reside in the adipose vasculature. Science 322: 583-586, 2008.

Calorie-Burning Fat Found in Lean Adults: New research has revealed that an energy-burning form of fat is active in adults—a finding that may open new avenues for efforts to combat obesity, a strong risk factor for type 2 diabetes. Unlike "white fat," which stores energy and comprises most body fat, another type of fat, called "brown fat," burns calories to help keep animals warm. In humans, it has been thought that brown fat is active only in infants. Now, using advanced imaging technology (PET-CT scans), a new study has found evidence that a significant portion of adults retain metabolically active brown fat. In this study, researchers detected substantial amounts of active brown fat in the neck region of adults. They also found some key differences among people. Women were more than twice as likely as men to have substantial amounts of this fat. Older people tended to have less brown fat, but being thinner was associated more with having brown fat, especially among older people—suggesting that brown fat may help protect against age-related weight gain. Interestingly, the researchers also observed that a person's brown fat changed with the outdoor temperature, with the most brown fat activity detectable in colder weather. This finding is consistent with two other research studies (funded in Europe) that were published at the same time, which showed that brown fat activity increased in people briefly exposed to cold. These clinical findings dovetail with recent insights in animal models into the molecular signals controlling the growth of brown fat. Together, these discoveries may help scientists develop therapeutic drug interventions to promote weight loss through increasing brown fat, or to exploit the finding that brown fat is activated by exposure to cold temperatures.

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Fat That Might Make Us Thin: A recent study has determined that a type of fat normally found in blood can help control hunger and food intake. Appetite is partially regulated by specialized regions of the brain so that energy intake (food calories) is balanced with energy expenditure. Hormones, nutrients, and other factors interact with the brain to mediate both short- and long-term feeding behavior. Fats circulating in the blood are also thought to help regulate appetite by interacting with the brain. However, it is unclear how this is accomplished.

In rats, scientists observed that a relatively abundant type of fat, called NAPE, is secreted into the blood from the small intestine after the animals are fed a meal containing high levels of dietary fats. Until this time, NAPE did not have a known physiological function. When the rats ate a meal containing a high level of fat, scientists observed a 60 percent increase in NAPE in the rats' blood. To make certain that the significant increase in NAPE was due to the dietary fat, the rats were injected with a solution of fat, glucose, or protein. Rats that were injected with fat had a 50 percent increase of NAPE in their blood while the animals injected with protein or glucose had no increase in NAPE levels. In addition, the elevated NAPE levels in the fat-injected animals persisted for 6 hours. To confirm the role of NAPE in appetite regulation, the researchers injected the rats with NAPE. Animals that were injected with different amounts of NAPE decreased their food intake accordingly. Rats that received a large amount of NAPE ate no food over a 12-hour period, whereas rats that were injected with a small amount of NAPE slightly decreased the amount they ate. Next, researchers examined the link between the brain and NAPE. Injecting NAPE directly into the brains of mice drastically reduced the animals' food intake for 12 hours. Additionally, the researchers found that NAPE circulating in the blood is able to enter the brain and accumulates in the hypothalamus, a part of the brain associated with regulating metabolism, digestion, and appetite. Furthermore, increased levels of NAPE in the blood of mice increased the activity of a specific kind

of neuron in the hypothalamus that controls hunger and food intake.

The ability of NAPE to control diet-induced obesity was highlighted by measuring NAPE production in rats that were fed a high-fat diet or their regular, lower-fat chow for 1 month. Subsequently, all the rats were given a high-fat meal, and then the amount of NAPE circulating in the blood was measured. Animals that had been fed the lower-fat diet had a significant increase in their plasma NAPE levels after eating the high-fat meal. Surprisingly, mice that had been fed the high-fat diet for a month were not able to increase their plasma NAPE concentrations following a high-fat meal. However, when the rats that consistently ate a high-fat diet were injected with NAPE, they significantly reduced their food intake. Finally, the researchers observed that infusions of NAPE also reduced body weight in the rats. These studies highlight the important link between NAPE and the ability to control hunger and food consumption in rodents. If this newly identified role for NAPE turns out to be similar in people, then this finding will have implications for a new strategy for treating diet-induced obesity.

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CONSEQUENCES OF EXCESS FAT

Maternal High-Fat Diet During Pregnancy Triggers Liver Disease in Offspring: A new study highlights a risk of liver disease resulting from exposure to excess fat and calories during fetal development. Childhood obesity has been correlated with the dramatic rise in incidence of type 2 diabetes and nonalcoholic fatty liver disease among youth in the U.S. Previous studies have shown that high-fat diets, obesity, and diabetes during pregnancy are associated with metabolic problems in the offspring. However, the mechanisms for these findings remain not well understood, and it can be difficult to distinguish between the effects of obesity and the effects of a diet that could lead to obesity. Current dietary guidelines for mothers with gestational diabetes include substituting fats for carbohydrates in the diet to help lower blood glucose levels. However, the results from this study suggest the importance of considering potential adverse effects of excess dietary fat when adjusting a diet.

Scientists recently explored the effects of a high-fat diet during pregnancy on liver disease in offspring, using an animal model in which some mothers were more susceptible to obesity and diabetes than others. These studies, done in non-human primates, suggest that a chronic high-fat diet results in a significantly increased risk of fetal fatty liver disease that persists after birth. This finding held true whether or not the mothers were themselves obese or had diabetes. Pregnant animals fed a high-fat, high-calorie diet produced offspring that had a three-fold increase in triglyceride fat in the liver. Furthermore, the offspring displayed evidence of increased liver stress during gestation, consistent with the development of fatty liver disease. Elevated levels of triglycerides persisted in the offspring following birth. Additionally, as the offspring grew, those from mothers fed a high-fat diet had a two-fold increase in percent body fat compared to offspring of mothers who ate a standard diet. Importantly, after female animals were consistently fed a high-fat diet for 4 years, switching them to a lower calorie, low-fat diet reduced fetal liver abnormalities in their subsequent offspring, even though some of the mothers remained obese and insulin-resistant. These studies suggest that a maternal high-fat diet may result in increased fat transfer to the fetus, and that unhealthy levels of fats in maternal blood (rather than diabetes or obesity) could potentially be the predominant cause of some future metabolic disorders in offspring. However, it is also possible that the health effects observed in offspring were the result of the high total calories fed to their mothers, rather than the percentage of calories from fat.

Fatty liver disease is an increasingly important cause of liver failure. Recognition of the role of the prenatal environment in the genesis of fatty liver provides a potential intervention to prevent the disorder. By shedding new light on dietary contributors to adverse health conditions, this study can direct future research efforts toward developing strategies to preempt disease.

McCurdy CE, Bishop JM, Williams SM, Grayson BE, Smith MS, Friedman JE, and Grove KL: Maternal high-fat diet triggers

lipotoxicity in the fetal livers of nonhuman primates. J Clin Invest 119: 323-335, 2009.

How Excess Lipid Leads to Cell Death: A recent study has shed new light on how fat causes cells to die, implicating a gene called *gadd7* and the molecule it encodes—a form of RNA. Cells react to extreme or prolonged stress, such as metabolic imbalances, physical injury, or improper protein folding, by activating pathways that lead to cell death. Lipids are normally stored in fat tissue that contains cells specifically designed for this function. When the amount of lipid exceeds the storage capacity of fat tissue, as seen in obese patients, lipid accumulates in locations other than fat tissue, such as the liver, kidneys, pancreas, or muscle. Improper lipid storage can lead to abnormal cell function, cell death, and organ failure, a condition called "lipotoxicity." Organ damage due to lipid storage in areas other than fat tissue is associated with the production of "free radicals"—highly reactive forms of oxygen molecules that cause damage to cells. Damage to cells by free radicals is known as "oxidative stress." Scientists have observed that feeding large amounts of saturated fat to cells isolated in the laboratory causes the cells to die due to oxidative stress. However, it is unclear precisely how excess fat leads to oxidative stress and cell death.

Researchers discovered that cells containing a defective version of the *gadd7* gene are resistant to cell death due to lipotoxicity when grown in liquids containing high levels of fat. To explore the molecular mechanisms underlying lipotoxicity, scientists generated mutant cells that could withstand excess saturated fat. These cells turned out to have a defect in the *gadd7* gene, and the scientists thus surmised that the normal form of *gadd7* must be involved in lipotoxicity. This gene was known previously to encode an RNA molecule, which it produced in response to exposure to hydrogen peroxide, a free radical. In the current study, when cells were incubated in high levels of fat, *gadd7* RNA levels increased in response to the lipotoxic environment and the subsequent generation of free radicals in the cell. If the cells were given antioxidants, both free radical and *gadd7* RNA levels were significantly reduced. The survival of the *gadd7* mutant cells in lipotoxic conditions was not due to an inability of the cells to take up fat from their environment. To confirm that *gadd7* plays a role in facilitating lipotoxic-induced cell death, the researchers created cells that produce levels of *gadd7* RNA significantly lower than normal. Reducing cellular levels of *gadd7* RNA led to protection against cell lipotoxicity when the cells were grown in the presence of high levels of fat. Furthermore, reducing *gadd7* RNA levels in the cells also led to a decrease in another characteristic cellular response to excess lipids—damage to the endoplasmic reticulum, a key component of the cell.

Taken together, these experiments demonstrate that *gadd7* RNA serves as a regulator for lipid-mediated oxidative stress and cell death. Although the precise manner by which *gadd7* affects lipotoxicity is not yet known, the data point to *gadd7* as a key mediator of cellular damage caused by oxidative stress. This is a unique function for an RNA molecule, and may serve as a potential target for therapies directed toward combating obesity-related diseases.

Brookheart RT, Michel CI, Listenberger LL, Ory DS, and Schaffer JE: The non-coding RNA gadd7 is a regulator of lipid-induced oxidative and endoplasmic reticulum stress. J Biol Chem 284: 7446-7454, 2009.

OBESITY, DIABETES, AND URINARY INCONTINENCE

Urinary Incontinence in Women Who Have Type 2 Diabetes and Are Overweight: Researchers have recently reported that urinary incontinence is highly prevalent among overweight and obese women with type 2 diabetes, and far exceeds the prevalence of other diabetes complications among this population. Using a self-report questionnaire, 2,994 women enrolled in the Action for Health in Diabetes (Look AHEAD) study indicated their frequency and type of incontinence within the last year. Analysis of the data revealed that weekly incontinence, experienced by 27 percent of participants, was reported more often than other diabetes-associated complications such as blood vessel changes in the eye, nerve pain, or protein in the urine. Furthermore, urinary incontinence affected non-Hispanic whites more than Asians or African Americans. Among the cohort, obesity was found to be the strongest modifiable risk factor for urinary incontinence. Another NIDDK-supported

study, the Program to Reduce Incontinence by Diet and Exercise (PRIDE), recently demonstrated that modest weight loss reduces urinary incontinence episodes in overweight and obese women who do not have diabetes. Ongoing research efforts by Look AHEAD investigators will reveal whether weight loss also reduces urinary incontinence among women with type 2 diabetes.

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RESEARCH ON BARIATRIC SURGERY

Evaluating the Safety of Bariatric Surgery: The Longitudinal Assessment of Bariatric Surgery (LABS) consortium conducted a multicenter, observational study to evaluate the 30-day safety outcomes in patients who underwent an initial bariatric surgical procedure. Approximately one-third of U.S. adults are considered obese based on their body mass index or BMI (a measure of weight relative to height); these individuals have increased risk for type 2 diabetes, coronary heart disease, stroke, fatty liver disease, certain types of cancer, and other diseases. Bariatric surgery is considered appropriate for those who are extremely obese (BMI of 40 or more) or those with a BMI of 35 or more who have significant obesity-related conditions, such as type 2 diabetes or sleep apnea. Approximately 6 percent of U.S. adults are extremely obese. Used as a treatment for extreme obesity, bariatric surgical procedures modify the digestive tract to limit the amount of food that can enter the stomach, decrease absorption of nutrients, or both. Currently, bariatric surgery appears to be the only intervention that consistently results in substantial and sustained weight loss in people who are extremely obese, and it has been linked to remission of type 2 diabetes, decreases in cardiovascular risk factors, and a significant reduction in mortality over time. Like most surgical procedures, however, bariatric surgery presents risks of complications and death that must be considered when deciding whether to undergo the procedure.

In this study, LABS-1, the consortium followed 4,776 patients who had bariatric surgery, from before their surgery through the first 30 days following surgery, to evaluate death and complication rates. All of the patients participating in the study were adults and were obese, and most had a BMI measurement reflecting extreme obesity. Similar to most populations undergoing bariatric surgery, the majority of the patients in the LABS-1 study were white and female. The study took place over 2 years at 10 medical centers located throughout the U.S., with one center coordinating data collection and analysis. Within 30 days of surgery, 4.1 percent of patients had at least one major adverse outcome, defined as development of blood clots in the deep veins of the legs or the pulmonary artery of the lungs, repeat surgeries, not being discharged from the hospital within 30 days, or death. Mortality rates were low: less than 1 percent (0.3 percent) of patients died within 30 days. The risk of complications varied depending on whether or not patients had certain health conditions prior to the surgery and how obese they were. Although the rate of adverse events also appeared to vary with the type of surgical procedure, differences in patient characteristics may have accounted for much of the variation in risk among the procedures. Further investigation may help clarify any such differences.

This evaluation highlights the level of short-term risks associated with bariatric surgery, an effective weight loss procedure that is increasingly popular as a treatment for extreme obesity. The safety of such surgery is an important consideration with risks examined in the context of long-term benefits. The LABS-1 study will help health care providers and patients make personalized decisions about the potential risks and benefits of bariatric surgery by taking into account a patient's characteristics. Another study being conducted by the LABS consortium, LABS-2, will follow a subset of the patients to gather longer-term data that will further inform decisions about the surgery.

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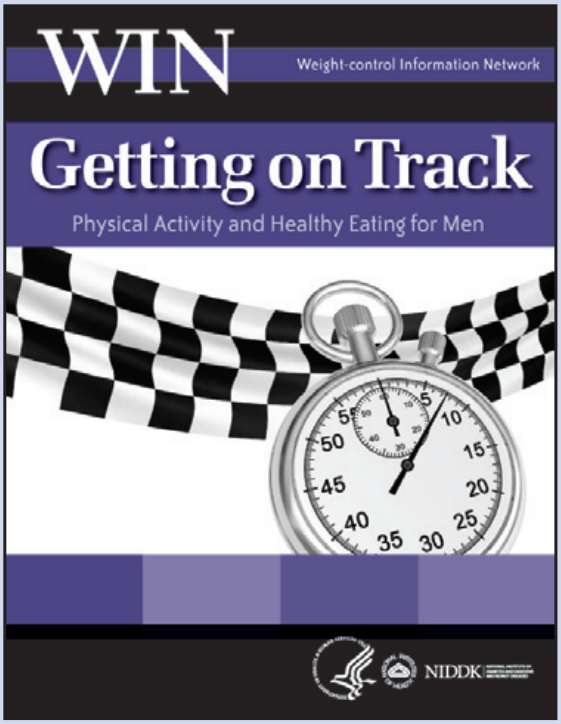
A WIN-Win Situation—The Weight-control Information Network's Getting on Track: Physical Activity and Healthy Eating for Men

The Weight-control Information Network (WIN), a national information service of the NIDDK, has developed a new brochure specifically for men entitled "Getting on Track: Physical Activity and Healthy Eating for Men." A significant number of U.S. adult men age 20 or older are overweight or obese based on body mass index (BMI), a measure of weight relative to height. Obese and overweight individuals have increased risk for developing serious diseases, including type 2 diabetes, cardiovascular disease, stroke, fatty liver disease, and certain types of cancer, compared to individuals of normal weight.

Moreover, there are gender-specific obesity-related health risks among obese men and women. Overweight men have greater overall health risks compared to overweight women, particularly during middle age. Although men typically have less body fat compared to women, they tend to store excess fat around their abdomen ("visceral fat"). Excess visceral fat substantially increases the risk of heart disease, metabolic syndrome, and type 2 diabetes.

To help men get fit and lose weight, WIN has published a new brochure, *Getting on Track: Physical Activity and Healthy Eating for Men*. In addition to providing information on BMI and risks associated with overweight and obesity, the brochure also includes information to help men "get on track" with healthy habits. These include tips to become more active (*e.g.*, walking daily, weight training, or taking the stairs rather than the elevator) and improve eating habits (*e.g.*, through increasing consumption of fruits and vegetables, and reducing portion size.) Additionally, the brochure explains how to set goals for safe and effective weight loss, offers tips on how these goals can be reached, and contains additional resources on weight loss for men.



This new brochure for men complements a variety of other publications that WIN has developed for men, women, and children. WIN was established in 1994 to provide the general public, health professionals, the media, and Congress with up-to-date, science-based information on obesity, weight control, physical activity, and related nutritional issues.

The copyright-free full text of *Getting on Track: Physical Activity and Healthy Eating for Men* is available online at: *www.win.niddk.nih.gov/publications/gettingontrack.htm*. Other WIN publications are available at: *http://win.niddk.nih.gov/*

STORY OF DISCOVERY

The Surprising Features of Fat

The body's adipose tissue—or fat—sustains life in times of famine, and it fuels physical activity and vital biological processes. Too much fat, however, is a recipe for metabolic disaster. For decades, scientists recognized that obesity is linked to type 2 diabetes and other diseases, but it wasn't clear why. After years of research, supported in large part by NIDDK, scientists now know that adipose tissue not only stores energy, it also sends signals to other parts of the body and the brain to regulate—or in the case of obesity, disrupt—metabolism. This research is informing the development of new therapeutic strategies.

Fuel for the Body: Fat Storage

Fat cells, also called adipocytes, harbor the body's energy reserves in droplets of lipids, or fat molecules. Previously, fat tissue was thought to be simply a storage area. However, there were hints that not all fat tissue is the same, and that the amount of body fat is regulated. In 1950, scientists described some unusually obese mice whose size seemed to result from an unidentified gene defect. Years later, NIDDK-supported researchers in the 1980s and early 1990s found that genetic factors influence people's propensity for excess weight gain as well as their body fat distribution—or where on the body an extra helping of dessert might end up. Studies also confirmed earlier observations that fat in certain locations confers heightened risk for type 2 diabetes. Researchers now refer to this particularly problematic fat as "visceral" fat—fat around the organs deep within the abdomen. In 1990, scientists in NIDDK's Division of Intramural Research discovered a protein called perilipin that surrounds the lipid storage droplets and controls fat storage. Researchers have since identified a number of proteins related to perilipin, and have found that the synthesis and breakdown of lipid droplets are highly regulated. Complementing research on fat cell function, researchers also identified a master regulator of fat cell formation. With NIDDK support, scientists in the early 1990s discovered that the protein PPAR-gamma directs certain types of immature, precursor cells to develop into fat cells. More recently, scientists used PPAR-gamma as a marker to trace the lineage of adipocytes and identify where, within fat tissue, fat-cell precursors reside. NIDDK-funded scientists also recently discovered an intriguing link between fat storage and the bacteria and other microbes that reside in the gut; certain gut microbes, and their collective genomes, seem to promote obesity.

Not Just a Storage Bin: Molecular Discoveries Linking Excess Fat to Metabolism and Disease

In 1994, NIDDK-supported scientists identified the *leptin* gene—a discovery that would ignite an explosion of research into the control of appetite and body weight, shine a spotlight on the role of adipose tissue in regulating metabolism, and change perceptions about obesity. A mutation in the *leptin* gene caused extreme obesity in the mice observed decades earlier. Subsequent research has shown that leptin protein, a hormone released by fat cells, travels to a key control center in the brain to update the status of the body's energy stores and reduce appetite. It also has effects elsewhere in the body. For people who lack leptin due to very rare genetic mutations, administration of the hormone effectively treats their extreme obesity, returning their weight to normal. Demonstrating a genetic and hormonal basis for excess body weight, this research also underscored that appetite control could no longer be viewed as solely a "will power" issue. Leptin treatment is not effective for people who have more common forms of obesity (which do not result from leptin deficiency), likely because other organs and tissues become resistant to leptin's actions. Researchers are now finding variants in other genes

and regions of the genome that may contribute to more common forms of obesity.

Since the discovery of leptin, NIDDK-supported researchers have elucidated a complex network of signaling molecules—several (like leptin) made by fat cells—that regulate appetite and energy expenditure. For example, adiponectin, secreted by fat cells, helps the body respond to the hormone insulin. In obesity, abnormally low levels of adiponectin are associated with insulin resistance, which is a risk factor for and hallmark of type 2 diabetes. By contrast, elevated levels of another factor, called RBP4, are associated with insulin resistance, type 2 diabetes, and cardiovascular disease risk. RBP4 is secreted by adipocytes, particularly those that comprise visceral fat. In other studies, researchers found a relatively high level of visceral fat in children who were obese and had pre-diabetes (high blood glucose conferring risk for diabetes). The children also had more fat in their muscles and liver, where it can cause metabolic problems. Pursuing research on a different fat-related condition, scientists in NIDDK's Division of Intramural Research, industry, and elsewhere have collaboratively shown that leptin can be used to treat metabolic problems associated with lipodystrophy, a rare group of disorders characterized by lack of fat in areas of the body where it should be, and abnormal fat accumulation in tissues such as liver and muscle.

Inflammation and Co-Conspirators Within Fat Tissue

Among the factors secreted by adipose tissue, several promote chronic inflammation, which has been linked to type 2 diabetes and cardiovascular disease risk. In 2003, NIDDK-funded researchers made the surprising discovery, first in mice and then in humans, that these factors are not all made by fat cells. Some are produced by cells of the immune system, macrophages, which infiltrate fat tissue. For example, macrophages within adipose tissue are the primary source of the pro-inflammatory factor TNF-alpha. Levels of another factor, resistin, are increased in obesity and contribute to insulin resistance. Originally identified as a fat cell-derived factor in mice, resistin interestingly is secreted by macrophages in humans.

Mind over Matter, and Matter over Mind

While the brain integrates an array of signals to control appetite and body weight, adipose tissue not only signals the brain to report on fat stores, but also exerts striking control over the brain's architecture and activity, as shown over the past several years by NIDDK-supported research. Scientists studying rodents discovered that leptin is involved in developing neural connections in the brain. In humans, researchers using advanced neuroimaging techniques found that the sight of food elicited different patterns of brain activity in obese people before and after weight loss. Leptin administration reversed many of these changes, and thus may potentially help people maintain weight loss.

From Fuel to Furnace: "Brown" Fat Tissue

The adipocytes that store fat are called "white" fat cells. However, another type of fat, "brown" adipose tissue, burns fat to dissipate heat, and helps keep babies and small animals warm. While white adipose tissue stakes its territory in the body with a tenacity known all too well to those on a diet, brown fat tissue was thought to disappear after infancy in humans. In 2009, however, NIDDK-supported scientists and other research teams discovered that brown fat is present in adult humans and appears metabolically active with exposure to cooler temperatures. They also found that people who are overweight or obese have less active brown fat. In studies in rodents, NIDDK-funded scientists are illuminating the molecular pathways that trigger brown adipocyte development. These experiments revealed that at least some brown fat can arise from the same precursor cells as another energy-burning tissue—muscle. Other brown fat cells may share a lineage with white adipose cells. These findings may lead to

a novel strategy for treating obesity: generating more brown fat cells to burn excess calories.

Future Directions

These discoveries about the multifaceted nature of fat tissue have revolutionized thinking about obesity and elucidated potential targets for future therapeutic development. As scientists advance technology for studying adipose tissue and measuring its effects in animal models and humans, new insights will emerge, along with new strategies to reduce excess fat and prevent the serious diseases associated with obesity.